12. **(NEW)** The process according to claim 9 wherein the DNA sequence functioning as a promoter is the DNA sequence coding for human platelet glycoprotein IIb (GPIIb).

13. **(NEW)** The process according to claim 9 wherein the hematopoietic cells are platelets.

14. **(NEW)** The process according to claim 5 wherein the hematopoietic cells are platelets.

REMARKS

Upon entry of this Amendment and Response, claims 1 to 14 are pending. Claims 1 to 7 have been amended to more clearly define the invention and new claims 8 to 14 have been added. Support for the amendments to claims 1 to 7 can be found in the specification and particularly at page 2, lines 24-26. Support for new claims 8, 13, and 14 can be found in the specification at page 1, lines 22-23. Accordingly, no new matter has been added.

Rejection Under 35 U.S.C. § 112, second paragraph

The Office has rejected claims 1 to 7 under 35 U.S.C. § 112, second paragraph "as being indefinite for failing to particularly point out and distinctly claims the subject matter which applicant regards as the invention." (*See* Office Action, p. 2.)

Applicants respectfully traverse. However, merely to expedite prosecution, Applicants have amended claims 1 to 7. Accordingly, the rejections should be withdrawn.

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Rejection Under 35 U.S.C. § 103

The Office has rejected claims 1-3 and 5-7 under 35 U.S.C. § 103(a) as "being unpatentable over Hao et al. (Human Gene therapy (July 1995) 6: 873-880) in view of Uzan et al. (J. Biol. Chem. (1991) 266(14): 8932-8939)." (*See* Office Action, p. 4.)

According to the Office, it would have been obvious to one of ordinary skill in the art to "modify the DNA construct for the expression of factor IX as taught in Hao et al. such that it contained the hematopoietic specific promoter, GPIIb, characterized in Uzan et al. and use the DNA construct in a method of making factor IX as taught in Hao et al." (*See* Office Action, p. 5.) Apparently, one of skill in the art would be motivated to combine the teachings of Hao and Uzan because "Hao et al. teaches that DNA constructs comprising a hematopoietic-specific promoter and a sequence coding for Factor IX are desirable for potential use in transfecting hematopoietic cells to be used in the treatment of hemophilia because they are more readily obtained than other cells, such as hepatocytes (see p. 878, Discussion, paragraph bridging Col. 1 and 2.)." (*See* Office Action, p. 5.) Applicants respectfully traverse.

As set forth in M.P.E.P. § 2143.01, in order to establish a *prima facie* case of obviousness the Office must meet three criteria. "First, there must be some suggestion or incentive, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (M.P.E.P. § 2143.01 and cases cited therein.)

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As explained below, the Office has failed to establish a *prima facie* case of obviousness because one of skill in the art would not be motivated to combine the teachings of Hao and Uzan. Further, the skilled artisan would not reasonably expect to succeed in expressing factor IX in hematopoietic cells using a hematopoietic-specific promoter if he were to combine Hao and Uzan. Accordingly, the rejection should be withdrawn.

Hao's experiments involved three specific promoters, the CMV promoter, the SV40 promoter, and the MoMuLV long terminal repeat, and a specific cell line, HL-60. (*See* Hao, Abstract; p. 875, "Results".) The amount of factor IX produced by Hao's different DNA constructs, shown in Table 1, demonstrate that not all promoters direct the construct to the HL-60 cells such that factor IX can be produced. Further, the production levels of factor IX are low, indicating poor expression. (*See* Hao, Table 1, p. 878.) Based on these results, Hao hypothesizes that "hematopoietic-specific promoters may result in persistent *in vivo* expression in the hematopoietic cells." (*Id.* at p. 879.)(Emphasis added.) Hao, however, does not know what type of hematopoietic cells to use (*see* Hao, p. 879 "It is not known which specific hematopoietic cell type(s) would be best for expression of factor IX."), but suggests phagocytes, lymphocytes, and erythrocytes. Hao does not suggest using megakaryocytes.

Further, Hao admits that "it is more difficult to achieve consistent expression of exogenous genes in primary, nontransformed cells than in immortal cell lines." (*See* Hao, p. 879.) Hao is essentially stating that they are unsure whether expression of factor IX in primary cells will work even if a hematopoietic-specific promoter were used.

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As the Office states, Uzan characterizes the GPIIb promoter and "suggests that this promoter can be used to target expression of heterologous genes in megakaryocytes." (*See* Office Action, p. 4.)(Emphasis added.) Uzan does not disclose the use of the GPIIB promoter in phagocytes, lymphocytes, or erythrocytes.

Based on this disclosure, one of skill in the art would be motivated by Hao to experiment with a variety of cell lines including phagocytes, lymphocytes, or erythrocytes, using some type of hematopoietic-specific promoter in order to express a DNA construct coding for factor IX. One of skill in the art, however, would not be motivated to use the GPIIb promoter, as disclosed in Uzan, in these experiments because Hao does not teach or suggest megakaryoctes and Uzan teaches the use of this promoter only in megakaryocytes. Accordingly, the Office has failed to establish a motivation to combine.

Further, the skilled artisan would not have any reasonable expectation of success (expression of factor IX in hematopoietic cells using the GPIIb promoter of Uzan) based on Hao's own statements. Thus, the combination of Hao and Uzan do not provide a motivation to combine with a reasonable expectation of success.

The Office has failed to establish a *prima facie* case of obviousness for at least the reasons stated above. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 1-3 and 5-7.

The Office has rejected claim 4 under 35 U.S.C. § 103(a) as being unpatentable over Hao, Uzan, as applied above, and further in view of Kurachi. (*See* Office Action, p. 5.) According to the Office, "it would have been obvious to one of ordinary skill in the art at the

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time of the invention to add an Intron I sequence of factor IX to a DNA construct comprising a tissue specific promoter and a sequence coding for factor IX as taught and suggested in Hao et al. and Uzan et al." (*See* Office Action, p. 6.) According to the Office, "[o]ne would be motivated to insert the Intron I sequence into the factor IX cDNA because, as Kurachi et al. teach, the first intron of Factor IX functions to enhance gene expression." (*See* Office Action, p. 6.) Applicants respectfully traverse.

As explained above, the Office has failed to establish a *prima facie* case of obviousness for claims 1-3 and 5-7, relying on Hao and Uzan. Kurachi, which is relied on for its disclosure of the first Intron I sequence of factor IX, does not cure the deficiencies of Hao and Uzan. Accordingly, the Office has failed to establish a *prima facie* case of obviousness for claim 4, which depends from claim 1. Applicants respectfully request the withdrawal of this rejection.

If there is any fee due in connection with the filing of this Statement, please charge the fee to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: February 27, 2002

By: _____
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APPENDIX

1. **(AMENDED)** **A** DNA-construct for the tissue-specific expression of a blood coagulation factor comprising a DNA **sequence** coding for an amino acid sequence of a blood coagulation factor and a DNA **sequence** **[**coding for**]** **functioning as** a promoter which is specific for **[the]** expression in hematopoietic cells.

2. **(AMENDED)** **The** DNA-construct as claimed in claim **[1]** **8**, wherein **[as]** **the DNA sequence functioning as a** promoter **is** the DNA **sequence** coding for **[**the**]** human platelet glycoprotein llb (GPllb) **[is inserted].**

3. **(AMENDED)** **The** DNA-construct as claimed in claim **[1]** **8** wherein the **[DNA coding for the amino acid sequence of an]** blood coagulation factor **[is the cDNA coding for]** **is** Factor IX.

4. **(AMENDED)** **The** DNA-construct as claimed in claim **[1]** **8**, wherein **[the]** **a** first truncated intron (Intron 1) of the human FIX gene **[has been]** **is** inserted **[additionally]** into the **DNA sequence coding for an amino acid sequence of a blood coagulation factor** **[FIX-cDNA].**

5. **(AMENDED)** **A** **[Process]** **process** for the production of Factor IX **[wherein the Factor IX is expressed]** in **[a]** hematopoietic **[cell line into which the DNA -construct of claim 1 has been transfected]** **cells comprising:**

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-transfecting hematopoietic cells with the DNA-construct of claim 3 and

-expressing the DNA-construct in the hematopoietic cells.

6. **(AMENDED)** **The** [Process] **process** as claimed in claim **[5]** **14,** wherein the production of Factor IX is stimulated by an inducer.

7. **(AMENDED)** **The** [Process] **process** as claimed in claim 6, wherein the **inducer** **[production of Factor IX]** is **[stimulated by]** phorbol-12-myristate-13-acetate (PMA).

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